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(71) Applicants
Yamanouchi
Pharmaceutical Co. Ltd.,
No. 5-1,
Nihonbashi-Honcho,
2-chome, Chuo-ku,
Tokyo, Japan
(72) Inventors
Tamio Hikosaka
Yutaka Konno
Masayoshi Aruga
(74) Agents
Reddie & Grose,
16 Theobalds Road,
London WC1X 8PL

(54) Improving taste acceptability of pharmaceutical compositions

(57) A medicinal composition which masks the objectionable taste of a water-soluble medicinal component thereof, comprises said objectionable-tasting water-soluble medicinal component, waxy material, and water swellable high molecular weight material. Suitable water-swellable materials include hydroxypropyl cellulose, carboxymethyl cellulose, carboxymethyl cellulose calcium salt, crosslinked polyvinyl-pyrrolidone, and pharmaceutically acceptable ion-exchange resins. Medicinal components include the hydrochloride salts of talampicillin, indenolol, hydralazine, and chlorpromazine. The composition is prepared by dispersing the other materials in the molten waxy material and solidifying, followed by grinding if necessary.

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SPECIFICATION

Medicinal composition

This invention relates to medicinal compositions containing water-soluble distasteful medicinal substances and to their production.

Bitter medicinal substances are usually administered in a form in which the bitterness is masked, e.g. as sugar-coated tablets, film-coated tablets, capsules, etc. However, there is a keen demand for such masked bitter medicinal substances in a convenient form for preparation, such as powder, fine granules, granules etc., and various attempts have been made to mask the bitterness of medicinal substances in such forms. In one such attempt a powder is produced by melting a waxy solid material having a melting point of about 40-100°C, dispersing the bitter medicinal substances in the molten material, and then (a) cooling and solidifying the dispersion by spraying it through a nozzle or (b) solidifying the dispersion by cooling followed by crushing; however on oral administration of a conventional composition so prepared, the medicinal substance is reluctant to dissolve in the mouth so that whilst the composition may mask the bitterness well it gives poor dissolution of the medicinal substance in the alimentary canal and hence reduces the bioavailability of the medicinal substance. For example, U.K. Pat. No. 1,323,161 discloses a method in which particles of a bitter medicinal substance are coated with a mixture (having a melting point higher than 95°C) of more than 50% hardened castor oil and less than 50% fatty acid having more than 16 carbon atoms; the medical composition obtained may mask the bitterness well but gives poor absorptivity of the medicinal substance.

To overcome this difficulty, it has been considered to compound the waxy solid material with a water-soluble material having a melting point of 40-100°C (e.g. polyethylene glycol, a sucrose fatty acid ester having high HLB, etc.,) but such water-suluble material does not uniformly mix with the waxy solid material even if they are mixed molten. Furthermore, compounding with a water-soluble excipient such as lactose, mannitol, etc., is scarcely effective for improvement of fault described above.

According to this invention, there is provided a medicinal composition which masks the objectionable taste of a water-soluble medicinal component thereof, the composition comprising said objectionable-tasting water-soluble medicinal component, waxy material, and water-swellable high molecular weight material.

There is also provided a method of producing such a composition which comprises dispersing a water-soluble medicinal substance of objectionable taste in molten waxy material together with water-swellable high molecular weight material and then solidifying the dispersion.

One or more waxing materials and one or more water-swellable high molecular weight materials may be used.

The medicinal substances used in the composition of this invention are those soluble in water and having objectionable taste, e.g. severe bitterness, but these is no particular restriction on the kind and range of them. Practical examples of them are talampicilline hydrochloride which is an antibiotic, indenolol hydrochloride which is a β-blocker, hydralazine hydrochloride which is an antidepressant, chloropromazine hydrochloride which is a transquilizer, etc.

Examples of the waxy materials used in this invention are waxes such as carbauba wax, beeswax, etc.; solid fats and oils such as castor wax, acetoglyceride, etc.; higher fatty acids such as stearic acid, palmitic acid, etc.; and high alcohols such as cetyl alcohol, stearyl alcohol, etc.

Examples of water-swellable high molecular weight materials used in this invention are hydroxypropyl cellulose of a low substitution degree (L-HPC), carboxymethyl cellulose or a calcium salt thereof, crosslinked polyvinyl pyrrolodone (PVPP), ion-exchange resins used for medicaments, etc.

In the method according to the invention the molten dispersion may for example be solidified by cooling by spraying through a nozzle or be solidified by cooling en masse and then ground into fine granules.

The proportion of waxy material is suitably more than 3 parts (by weight) to one part of the medicinal component and that of the water-swellable high molecular weight material is suitably 0.05-0.3 part to one part of the waxy material. If the compounding ratio of the waxy material is less, the viscosity of the dispersion obtained by dispersing the medicinal component and the high molecular weight material in the molten waxy material becomes high, which makes it difficult to obtain fine granules or particles by spraying the dispersion and hence to obtain well coated granules or particles. If the compounding ratio of the high molecular weight material is less, the swelling power and the dissolving effect become insufficient, while if the compounding ratio is too high, the viscosity of the dispersion becomes high and hence it becomes difficult to make fine granules or particles.

Various preparations may be produced using the composition of this invention by adding thereto conventional preparative excipient such as lactose, mannitol, etc., and, if necessary, other ingredients such as coloring agents, odorants, etc., or these preparations may be produced by adding the aforesaid components during the production of the composition.

To exhibit the effects of the compositions of this invention, organoleptic test results on bitterness and dissolution test results are shown in Table 1 together with comparison sample results.

Table 1

Test sample					Organoleptic test result	Dissolution test result (%)		
Example	*Medicinal substance*	*Waxy material*	*High molecular material*	*Weight ratio*		*30 min.*	*60 min.*	*90 min.*
Contrast 1	Talampicilline hydrochloride	Lubriwax	–	1:4	(–)	11.6	12.1	13.5
1	"	"	L-HPC	1:3:0.25	(–)	82.9	85.4	88.1
2	"	"	L-HPC	1:4:0.5	(–)	92.1	96.4	96.8
3	"	"	CMC Ca	1:4:0.5	(–)	91.5	96.3	97.2
4	"	"	Amberite	1:4:0.5	(–)	89.4	93.8	94.3
5	"	"	PVPP	1:5:1	(–)	96.3	98.5	98.2
6	"	Himako	L-HPC	1:5:1	(–)	90.3	93.4	94.1
Contrast 2	Hydralazine hydrochloride	Lubriwax	–	1:5	(–)	5.2	6.9	7.9
7	"	"	L-HPC	1:5:1	(–)	83.9	85.4	87.1
8	"	"	CMC Ca	1:5:1	(–)	81.8	84.5	87.7
Contrast 3	Indenolo hydrochloride	"	–	1:5	(–)	11.6	15.7	17.3
9	"	"	L-HPC	1:5:1	(–)	85.2	87.2	89.3
Contrast 4	Chloropromazine hydrochloride	"	–	1:5	(–)	35.0	36.7	34.8
10	"	"	L-HPC	1:5:1	(–)	87.9	95.5	96.6

Note:

(1) In the organoleptic test, (–) means that no bitterness was tasted.

(2) The measurement of dissolution was performed by adding 100 mg of the fine granules of the sample to a 100 milliliter bottle containing 50 ml of the Japan Pharmacopoeia 1st liquid of 37 ± 0.5°C, shaking the bottle in a constant-temperature bath at an amplitude of 3.5 cm and a frequency of 120 per minute, and then measuring the medicinal substance thus dissolved by absorptiometry.

(3) Comparison (contrast) samples 1, 2, 3 and 4 were produced by following the method as in Example 1.

The results shown in the above table indicate that the compositions of this invention gave no bitterness in the organoleptic test and at the same time showed excellent dissolution in comparison with the contrast compositions.

The compositions of this invention and their production are further explained by the following Examples.

Example 1

In 300 g of a hydrogenated vegetable oil (Lubriwax 102H, a trade name, made by Freund Industries Co., Ltd.) melted on an oil bath were uniformly dispersed 100 g of talampicilline hydrochloride and 25 g of L-hydroxyporpyl cellul se (L-HPC, a trade name, made by Shin-Etsu Chemical Co., Ltd.) and then the dispersion was sprayed in a room at temp ratures below 30°C by means of a rotary disc type atomiz r (made by Iwai Kikai Kogyo K. K.) to provide coated granules of 32-80 mesh.

Example 2

Talampicilline hydrochloride	100 g
Hydrogenated vegetable oil (Lubriwax 102H	400 g
L-Hydroxypropyl cellulose (L-HPC)	50 g

Coated granules were produced using the above components in the same manner as in Example 1

Example 3

Talampicilline hydrochloride	100 g
Hydrogenated vegetable oil (Lubriwax 102H)	400 g
Carboxymethyl cellulose calcium (ECG 505, a trade name, made by Gotoku Yakuhin Kogyo K. K.)	50 g

Coated granules were produced using the above components in the same manner as in Example 1.

Example 4

Talampicilline hydrochloride	100 g
Hydrogenated vegetable oil (Lubriwax 102H)	400 g
Ion exchange resin (Amberite IRP-88, a trade name, made by Rhóm and Haas Co.)	50 g

Coated granules were produced using the above components in the same manner as in Example 1.

Example 5

Talampicilline hydrochlorid	100 g
Hydrogenated vegetable oil (Lubriwax 102H)	500 g
Crosslinked polyvinylpyrrolidone (Kollidon CL, a trade name, mad by BASF A.G.)	100 g

Coated granules w re produced using th above comp nents in the same manner as in Example 1.

Example 6

Talampicilline hydrochloride	100 g
Hydrogenated vegetable oil (Himi Ko, a trade name, made by Kawaken Fine Chemical Co., Ltd.)	100 g

Coated granules were produced using the above components in the same manner as in Example 1.

Example 7

Hydralazine hydrochloride	100 g
Hydrogenated vegetable oil (Lubriwax 102H)	500 g
L-Hydroxypropyl cellulose (L-HPC)	100 g

Coated granules were produced using the above components in the same manner as in Example 1.

Example 8

Hydaralazine hydrochloride	*100 g*
Hydrogenated vegetable oil (Lubriwax 102H)	*500 g*
Carboxymethyl cellulose calcium (ECG 505)	*100 g*

Coated granules were produced using the above components in the same manner as in Example 1.

Example 9

Indenolol hydrochloride	100 g
Hydrogenated vegetable oil (Lubriwax 102 H	500 g
L-Hydroxypropyl cellulose (L-HPC)	100 g

Example 10

Chloropromazine hydrochloride	100 g
Hydrogenated vegetable oil (Lubriwax 102H)	500 g
L-Hydroxypropyl cellulose (L-HPC)	100 g

Coated granules were produced using the above components in the same manner as in Example 1.

CLAIMS

1. A medicinal composition which masks the objectionable taste of a water-soluble medicinal component thereof, the composition comprising said objectionable-tasting water-soluble medicinal component, waxy material, and water-swellable high molecular weight material.

2. A composition according to claim 1 wherein the proportion of waxy material is over 3 parts by weight to one part of objectionable-testing water-soluble medicinal component, and the proportion of water-swellable high molecular weight material is 0.05-0.3 part by weight to one part of waxy material.

3. A composition according to claim 1 or 2 wherein the waxy material is at least one material selected from waxes, solid fats and oils, higher fatty acids, and higher alcohols, and the water-swellable high molecular weight material is at least one of hydroxypropyl cellulose of low substitution degree, carboxymethyl cellulose, carboxymethyl cellulose calcium salt, crosslink d p lyvinylpyrrolidone, and medical i n-exchang resins.

4. A composition according to claim 1, 2 or 3, wher in the objectionable-tasting water-s luble medicinal component c mprises talampicilline hydrochl rid , indenolol hydr chloride, hydralazine hydrochloride, or chloropromazin hydrochloride.

5. A composition according to any preceding claim wherein the water-swellable high m lecular weight material comprises hydroxypropyl cellulose of low substitution degree.

6. A method of producing a c mpositi n according to claim 1 which comprises dispersing a water-soluble medicinal substance of objectionable-taste in molten waxy material together with water-swellable high molecular weight material and then solidifying the dispersion.

7. A method according to claim 6 wherein the molten dispersion is solidified by spray cooling.

8. A method according to claim 6 wherein the molten dispersion is solidified by cooling and then ground.

9. A composition produced by the method according to claim 6, 7 or 8.

10. A medicinal composition substantially as hereinbefore described in any one of Examples 1 to 10.

11. A medicinal preparation comprising a composition according to any of claims 1 to 5 and 10 in an excipient.

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